CME/CE ARTICLE

CUTANEOUS LEISHMANIASIS: BATTLING THE BAGHDAD BOIL

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As the number of cases increases, it's imperative that military and VA practitioners know how to evaluate and manage this infection in service personnel returning from endemic areas.

It's estimated that more than 350 million people in 88 countries on four continents are at risk for acquiring cutaneous leishmaniasis (CL), which has an estimated annual incidence of 1.5 to 2 million cases.[1] As the Global War on Terrorism stations U.S. troops and government contractors in endemic areas, the number of cases seen by U.S. health care providers is increasing. Over the past year, at Walter Reed Army Medical Center (WRAMC) in Washington, DC, we've evaluated numerous patients referred to our facility for the treatment of leishmaniasis, which they acquired while serving in Afghanistan or Iraq.[2]

WRAMC and Brooke Army Medical Center in San Antonio, TX are the only DoD facilities involved in investigational drug protocols pertaining to leishmaniasis treatment. As new troops deploy to the Middle

CONTINUING MEDICAL EDUCATION and CONTINUING EDUCATION

GOAL

To review the clinical signs and symptoms of cutaneous leishmaniasis (CL), discuss diagnosis, and provide a brief overview of selected treatment options.

OBJECTIVES

After reading this article and taking the appropriate test (CME on page 68 or CE on page 70), all physicians and other health care professionals should be able to:

1. Understand the pathophysiology of CL and its parasitic nature as compared to other cutaneous lesions.
2. Describe the collection techniques and diagnostic procedures used to identify CL positively.
3. Discuss the availability, efficacy, and adverse effects of the various treatment options used to combat CL.

ACCREDITATION

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This article has been peer reviewed and approved for CME credit by Louis M. Weiss, MD, professor of medicine and pathology at Albert Einstein College of Medicine, Bronx, NY. Review date: September 2004. **Dr. Weiss reports no conflict of interest.**

This article has been peer reviewed and approved for CE credit by Julie A. Hixson-Wallace, PharmD, BCPS, clinical associate professor and director of continuing education at Mercer University Southern School of Pharmacy, Atlanta, GA.

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CME test on page 68 CE test on page 70

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East and the number of affected patients increases, however, other DoD facilities and VA medical centers may need to become involved in evaluating returning service personnel. For these reasons, the U.S. Army Office of the Surgeon General has asked us to share our experience with other federal practitioners who may become involved in the diagnosis and management of leishmaniasis.

In this article, we'll review the clinical signs and symptoms of CL and discuss diagnosis. We'll also provide a brief overview of selected treatment options that are used in our facilities.

VECTOR AND PARASITE

Leishmaniae are sand fly-borne parasites that appear as intracellular amastigotes within the macrophage phagosomes of the mammalian host, and as extracellular flagellated promastigotes in the gut of the sand fly or in vitro culture. Many species of sand flies are vectors of leishmaniasis. The most common are the *Phlebotomus* species in the eastern hemisphere, or Old World, and the *Lutzomyia* species in the western hemisphere, or New World. Because of their relatively small size, sand flies may pass through some large weave mosquito netting—particularly if it hasn't been treated with an insect repellent, such as permethrin.

Generally, leishmaniasis is a zoonosis with humans acting as incidental hosts and other mammals (especially rodents and dogs) acting as reservoir hosts. There are, however, exceptions to this rule: Both *Leishmania tropica* and *Leishmania donovani* infection can be transmitted anthroponotically.[3]

PATHOPHYSIOLOGY

Leishmaniae are adept at escaping humoral and cellular immune responses. This is due, in large part, to their intracellular life cycle and ability to regulate the host T cell response.

Potential human infection begins when *Leishmania* metacyclic promastigotes are injected into the skin by the bite of an infected sand fly. Through receptor-mediated phagocytosis, these promastigotes are taken up into the mononuclear phagocytes where they transform into amastigotes.

The sand fly saliva contains a vasodilatory peptide, maxadilan, which seems to advance *Leishmania* infection by supporting parasite survival around the inoculation site.[4] Some surface antigens of *Leishmania*, such as glycoprotein 63 (a 63-kd, zinc-dependent metalloprotease) and lipophosphoglycan, enable the attachment and uptake by macrophage receptors—the receptor for complement, the receptor for mannose and fucose, and receptors for advanced glycosylation end products.[3] Dendritic cells are involved in the inhibition of an effective immune response, and dendritic cell-specific intercellular adhesion molecule 3 grabbing nonintegrin (DC-SIGN) appears to be a receptor.[5] The intracellular location of the *Leishmania* amastigote permits the parasite to subvert some of the usual functions of the infected white blood cell.

A humoral response does not seem to confer protection from the Leishmania pathogen, which has been shown to persist in its host after clinical cure.

Leishmaniae are destroyed by interferon-gamma activation of the macrophage through tumor necrosis factor-alpha induction of nitrous oxide synthase.[6] L-arginine–dependent nitrous oxide production is responsible for killing the parasites within the macrophages.[7] A humoral response does not seem to confer protection from the *Leishmania* pathogen, which has been shown to persist in its host after clinical cure. In the murine model, interleukin (IL)-10 was found to be necessary for chronic infection, while IL-10 deficiency permitted a sterile cure.[8]

Extensive study of the cellular immunity of leishmaniasis, predominantly using a murine model, suggested that host cytokine responses are critical early in infection. A cell-mediated immune response to *Leishmania major* may depend on a CD40-CD40 ligand process mediating an IL-12 response.[9] Research suggests that dendritic cells may play an essential role in this mediation.[10] In mice, T helper 1 cells expand during healing, while T helper 2 cells expand during progressive *Leishmania* infection.[11]

In humans and mice, IL-4 regulates T helper 2 cell differentiation, which then downregulates interferon-gamma production, IL-12, IL-12 receptor expression, and macrophage nitrous oxide.[12,13] In

humans, the cytokine and T cell responses appear to be more complex and differ among *Leishmania* species and with various leishmaniasis syndromes.

CLINICAL CLASSIFICATION

The clinical expression of leishmaniasis—in terms of tropism, invasiveness, and pathogenicity—depends on complex interactions between the host's immunologic responses and the particular *Leishmania* species. Generally, leishmaniasis is divided into three clinical syndromes: cutaneous, mucosal, and visceral infection. Cutaneous leishmaniasis is localized to skin. Mucosal leishmaniasis occurs mainly as a late complication in new-world CL and is associated particularly with infection by *Leishmania (Viannia)* species. Visceral leishmaniasis is caused predominately by *L. donovani* and *Leishmania infantum-chagasi*, though in the Persian Gulf War, *L. tropica* caused a mild form of visceral disease referred to as viscerotropic leishmaniasis.[14]

When the intracellular development of amastigotes remains at the inoculation site, cytokines are released and cell reactions result in the development of localized lesions.[3] Infection can be subclinical, subacute, chronic, or acute and progressive. In immunocompromised hosts, the character of the syndromes may modulate and species that are associated with localized infection (such as *L. major*) may disseminate.[15–17]

Typically, CL acquired in the Old World is caused by *L. major* and *L. tropica*. In Central and South America (the New World), *Leishmania mexicana* and members of *Leishmania (Viannia)*—such as *Leishmania (Viannia) braziliensis*, *Leishmania (Viannia) guyanensis*, and *Leishmania (Viannia) panamensis*—are the most common causes. To date, most CL acquired during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) has been caused by *L. major*.[2]

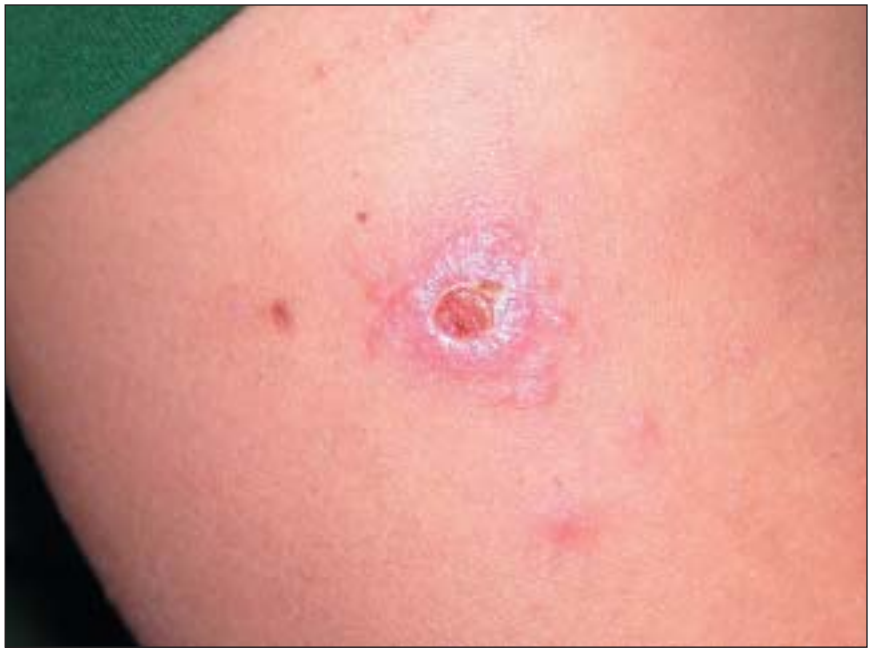

Figure 1. A typical lesion of old-world cutaneous leishmaniasis with a well circumscribed shallow ulcer and a raised, violaceous border. Also evident are small satellite papules.

Leishmaniasis can involve the skin in five ways, creating five distinct forms of CL: localized, disseminated, recidivans, diffuse, and post–kala-azar dermal leishmaniasis. Localized (that is, nondisseminated) CL is overwhelmingly the most common manifestation, the others being relatively rare.

Localized CL (also known as "Oriental sore" or "Baghdad boil") is usually a slowly developing inflammatory skin sore that heals spontaneously with scarring—typically within a year, though the rate of healing depends in part on the infective species.[18] The sore appears at the site of the sand fly bite (generally on areas of the body that are uncovered at night, such as arms, legs, face, neck, or ears) after two to eight weeks.

The leishmanial lesion may be nodular, plaquelike, or ulcerative. Characteristically, it begins as an asymptomatic, nonspecific erythematous papule, easily confused with any insect bite, and then enlarges slowly. The center usually softens and may ooze, often with crusting that comes off and is replaced recurrently, ultimately forming a well circumscribed, shallow ulcer—sometimes with a raised violaceous border or with concentric surrounding rings of desquamation (Figure 1).

Among 1,096 patients with acute, localized CL in Isafan, Iran, lesions took on various appearances, including hyperkeratotic, zosteriform, erysipeloid, sporotrichoid, eczematoid, and verrucous.[19] Given its variable appearance, CL has an

Table 1. Differential diagnosis for cutaneous leishmaniasis

- Bacterial infection
  - —Cutaneous anthrax, diphtheria, tularemi
  - —Tuberculosis
  - —*Treponema*
  - —*Staphylococcus* and *Streptococcus* species
  - —*Mycobacterium marinum* and other nontuberculin mycobacteria
  - —*Mycobacterium leprae*
- Fungal infection
  - —Blastomycosis
  - —Sporotrichosis
  - —Paracoccidiodomycosis
- Myiasis
- Sarcoidosis
- Skin cancer
- Ecthyma
- Pyogenic granuloma
- Allergic response to arthropod assault
- Brown recluse spider bite

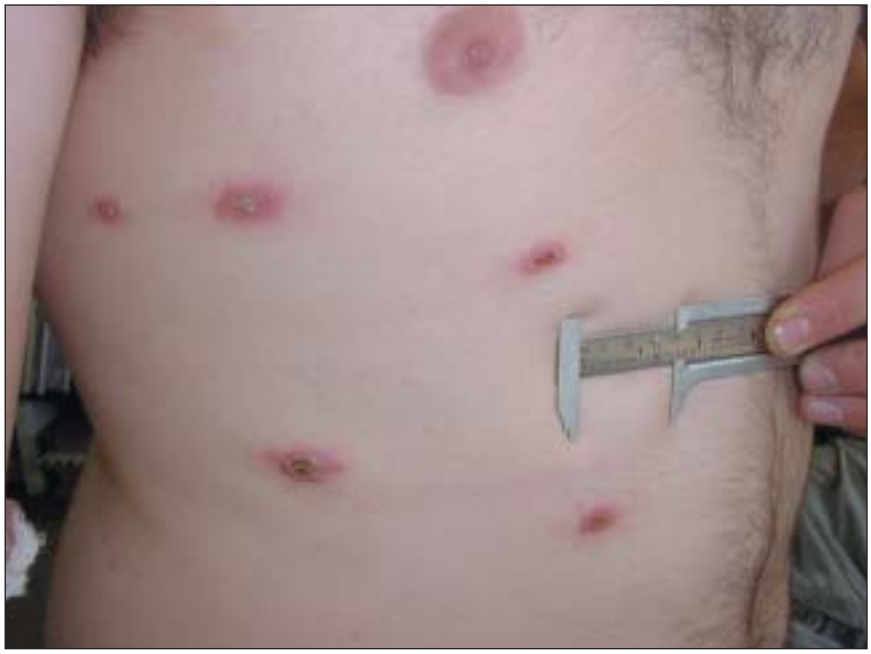

Figure 2. Old-world cutaneous leishmaniasis presenting as multiple lesions.

extensive differential diagnosis (Table 1) and should be considered in any patient who develops a chronic, persistent skin lesion after traveling to an endemic area.

The patient with CL often relates having many bites, most resolved and only a few further developed. In our experience with OIF patients, the median number of lesions was three; the range, one to 47 (Figure 2). The lesions tend to heal from the center outward, leaving an atrophic and pigmented, sometimes depressed, scar. The sore is usually painless but can be painful if large or secondarily infected. One variant noted in OIF patients at WRAMC has been olecranon bursitis forming underneath large psoriaform plaques on the elbows.

There are seven clinical features that correlate well with the diagnosis of old-world CL: exposed site location; pairing or clustering of lesions; orientation of the skin sore along the skin crease; volcanolike ulcer; inflammatory satellite papules no more than 2 cm from the edge of the primary lesion ("daughter nodules"); proximal, sporotrichoid, subcutaneous nodules; and subcutaneous induration extending underneath the skin lesion (Table 2).[20] Among these, signs of potential cutaneous dissemination include multiple daughter nodules, sporotrichoid subcutaneous nodules generally tracking toward regional lymphatics, or localized adenopathy.

A rare variant of CL is leishmaniasis recidivans, which is usually due to *L. tropica*. It presents as a chronic nonhealing or relapsing lesion that appears on or at the edge of a scar produced by a previous cutaneous ulcer. Onset is generally within two years of the original ulcer, but much later onset has been reported with trauma or topical steroid use.[21] Leishmaniasis recidivans, often called "chronic relapsing CL," also has been called "chronic lupoid leishmaniasis" because it resembles lupus vulgaris. In such cases, organisms rarely are identified through histopathologic examination, though parasite culture and polymerase chain reaction (PCR) testing may be helpful in confirming the diagnosis.

Diffuse CL is an unusual form of the infection, characterized by profuse parasitization and absence of an appropriate inflammatory response. It is caused mainly by *Leishmania aethiopica* in Africa and *Leishmania mexicana amazonensis* in the New World.

Table 2. Clinical features that correlate well with the diagnosis of old-world cutaneous leishmaniasis[20]

- Exposed site location
- Pairing or clustering of lesions
- Orientation of the skin sore along the skin crease
- Volcanolike ulcer
- Inflammatory satellite papules no more than 2 cm from the edge of a primary lesion
- Proximal subcutaneous nodules
- Subcutaneous induration extending underneath the skin lesion

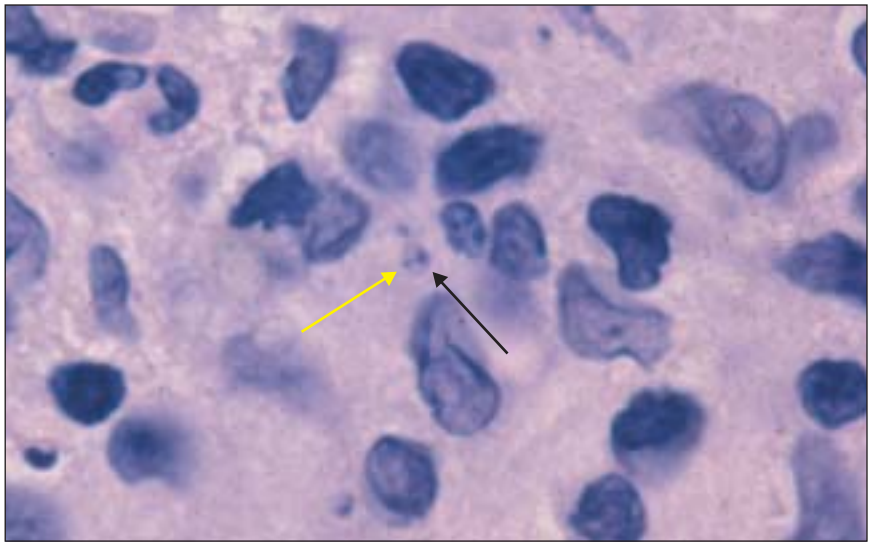

Figure 3. An amastigote (black arrow) with a kinetoplast (yellow arrow), hematoxylin-eosin stain, 300x.

Post–kala-azar dermal leishmaniasis consists of symmetric macules, papules, or nodules on the face—and sometimes on the trunk and extremities—of patients who have had visceral leishmaniasis. It's found in Africa, India, and (less frequently) the New World, usually in patients recovering from visceral leishmaniasis associated with *L. donovani*.

DIAGNOSING CL

CL is suggested by clinical features and confirmed by visualizing or culturing the parasite or demonstrating parasite DNA by PCR. Amastigotes are most abundant in new or diffuse CL lesions.[3,22] Conversely, they are noted infrequently in chronic or mucosal leishmanial lesions.[3] Collection techniques from skin lesions include lesion scraping, needle aspiration using injected saline, slit skin smear, and punch biopsy with tissue-impression smears made from a biopsy sample by rolling the cut portion on a slide after blotting excess blood.[23] Some of the collected sample may be smeared onto glass slides and stained with Diff-Quik (Dade Behring Inc., Newark, DE) or Giemsa stain (Medical Chemical Corporation, Torrance, CA) and examined for amastigotes under oil immersion microscopy.

Amastigotes multiply within the vacuoles of macrophages and can be found in aggregates. The amastigote is a round to oval body about 1.5 to 4 µm in diameter. It consists of a cell membrane, cytoplasm, an internal nucleus, and a rod-shaped kinetoplast (Figure 3). With Giemsa staining, the amastigote cytoplasm is blue, the nucleus violet-blue, and the kinetoplast reddish to violet in color.[18] To diagnose leishmaniasis, you must see the kinetoplast. Otherwise, *Histoplasma capsulatum* could be mistaken for *Leishmania*.

In recent cases of localized CL at WRAMC, full thickness punch biopsies were not as easy to interpret through microscopic examination as were skin scrapings (Figure 4). An adequate scraping provides a deep dermal collection of many parasites without the dense background seen in skin biopsies.[23] The advantage of a punch biopsy is that it allows for the diagnosis of conditions other than leishmaniasis, so punch biopsy is recommended as a secondary procedure if the initial scrapings are unrevealing. The classic recommendation for biopsy site is the active border of the lesion, though this has been challenged by a Guatemalan study suggesting that the middle of the lesion yields similar results.[24]

The histopathologic changes of early, localized CL are characterized by a diffuse infiltrate of lymphocytes and monocytic leukocytes with rare granuloma formation.[25] Parasite-laden macrophages often are found in the upper dermis. Tissue sections need to be cut very thinly (4µm) and examined using the oil immersion objective. Hematoxylin-eosin staining is usually

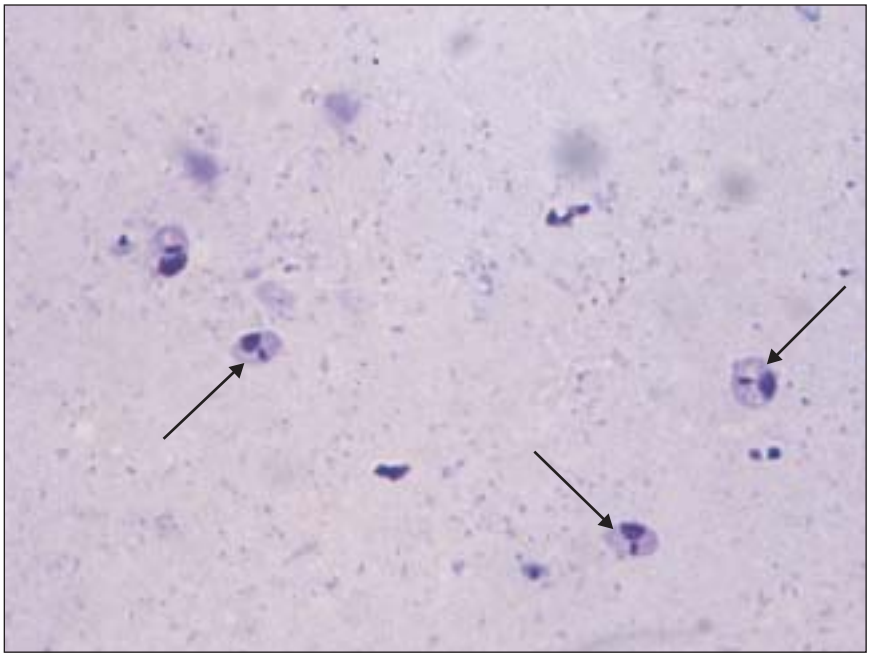

Figure 4. Three amastigotes in skin scrapings, Giemsa stain, 300x.

Table 3. "At risk" old-world cutaneous leishmaniasis

- Lesions over joints where scarring would impede future range of motion
- Multiple or large lesions
- Cosmetically unacceptable lesions
- Lesions associated with potential dissemination (adenopathy, subcutaneous nodules, satellite lesions)
- An immunocompromised host
- Chronic lesion unhealed after many months
- Mucosal involvement

adequate to demonstrate amastigotes. According to COL Peter McEvoy, MC, USA, chief of the division of infectious and tropical diseases pathology at the Armed Forces Institute of Pathology in Washington, DC (oral communication, April 2004), the Brown-Hopps tissue gram stain may accentuate the kinetoplast. As the lesion becomes more chronic, noncaseating granulomas with epithelioid cells and Langhans' giant cells are present. Follicular plugging, pseudoepitheliomatous hyperplasia, atrophy, hyperkeratosis, and basal cell degeneration may be present, but are nonspecific.[25]

For culture, skin specimens should be inoculated into Novy-MacNeal-Nicolle biphasic or supplemented Schneider's insect media. Culture of leishmaniae permits species identification using isoenzyme electrophoresis. A disadvantage of this diagnostic method is that motile promastigotes may appear in the culture anywhere from one day to one month later depending on the growth characteristics of the particular parasite. In difficult to diagnose cases, animal inoculation can be obtained.

The leishmanin (Montenegro) skin test is performed by injecting intradermally killed promastigote antigen to produce a cutaneous, delayed hypersensitivity reaction. The test, however, cannot distinguish between active and past infections, and it's not available or used in the United States.

Molecular techniques such as PCR are used increasingly for diagnosis.[26] The real-time PCR platform produces results within hours.[27] Various amplification targets have been used, including kinetoplast, telomere, and nuclear DNA as well as ribosomal RNA. While fresh tissue is preferable, paraffin-embedded tissue also can be used.

For patients whose infection was acquired through military service and for military health care dependents, the Leishmaniasis Diagnostic Laboratory (LDL) at Walter Reed Army Institute of Research in Silver Spring, MD can assist in diagnosis. The LDL may be contacted at the following telephone number: (301) 319-9956. A research PCR assay is available on a consultative basis from the LDL.

SYSTEMIC THERAPY

The standard treatment for new-world and "at risk" old-world CL (Table 3) consists of parenteral administration of a pentavalent antimony (PVA) compound—either meglumine antimoniate or sodium stibogluconate. Although PVAs have been used for more than 50 years, none has been approved by the FDA. PVAs can be used only under an investigational new drug (IND) research protocol in the United States. Sodium stibogluconate can be accessed for military patients at one of two leishmaniasis

treatment centers: WRAMC, Washington, DC or Brooke Army Medical Center, San Antonio, TX. For civilian patients, sodium stibogluconate can be acquired by physicians from the CDC Drug Services section.

At the currently recommended dosage of 20 mg/kg/day for 20 days, PVAs have variable efficacy. Depending on the species of *Leishmania* being treated, their efficacy ranges from 45% to 100%.[20,28–30] Common adverse effects include elevation of pancreatic and liver enzymes, arthralgia, and myalgia—all of which are usually reversible.[28,31] Fatal pancreatitis has been reported, however.[32] And there have been reports of thrombocytopenia, leukopenia, anemia, rash, anorexia, headache, fatigue, gastrointestinal symptoms, and reactivated herpes zoster as well.[28,33,34] The most common electrocardiographic effects are ST segment and T wave changes. Prolongation of the corrected QT interval to more than 0.5 second is an indication to discontinue therapy temporarily.[28,35]

Oral imidazole compounds have been used systemically for CL, and studies demonstrate that their efficacy is largely dependent on the *Leishmania* species involved. Ketoconazole has been used successfully to treat CL caused by *L. major* and *L. mexicana* but is less effective against *L. tropica*, *L. aethiopica*, and *L. braziliensis*.[36,37] A randomized, controlled trial using itraconazole 7 mg/kg/day for three weeks to treat *L. major* showed it did not differ significantly from placebo in its effect (59% versus 44% healing).[38] By contrast, in a randomized, controlled trial using oral fluconazole 200 mg/day for six weeks to treat *L. major*, the fluconazole treatment group demonstrated significantly greater healing at three months than the placebo group (59% versus 22%), and the time to complete healing was three weeks shorter for the fluconazole treatment group.[39]

There are very few randomized, controlled trials of allopurinol in old-world leishmaniasis, and usually, it's been studied in combination with a PVA. One study compared allopurinol with a low dose PVA alone and with a low dose PVA used in conjunction with allopurinol. The addition of allopurinol significantly increased the response rate, but the healing rate for allopurinol alone was only 18%.[40] Another study of patients with new-world (American) leishmaniasis (not the type that military personnel are acquiring in Iraq and Afghanistan) demonstrated no benefit.[41]

New lipid-associated amphotericin compounds theoretically should target *Leishmania* organisms because the amphotericin B-lipid complexes are cleared from blood by the monocellular, macrophagic system in which the parasite persists. It's questionable, however, whether they achieve sufficient concentration in the skin to be effective.[42] None of these preparations has been tested against conventional amphotericin B, and they are FDA-approved only for visceral leishmaniasis at this time.

LOCAL THERAPY

Parenteral antimony injections may be inconvenient and may expose patients to toxicity. Local treatment of cutaneous lesions, therefore, is preferable. If there are no signs of localized dissemination, the lesions are of modest size and number, and the species is not associated with late mucosal or visceral complications, local therapy can be considered.

Topical paromomycin (also known as aminosidine) mixed with methylbenzethonium chloride has been used to treat *L. major* with reported efficacy of 74% at 10 to 20 days.[43] There have been subsequent randomized, controlled trials in which preparations without methylbenzethonium chloride were not as effective as those containing methylbenzethonium.[44] Currently, topical paromomycin treatment is not approved by the U.S. FDA.

Leishmania parasites are known to be thermosensitive, and for this reason, both heat and cold treatments have been tried.[45–50] In a placebo-controlled trial that compared the effects on new-world CL of three heat therapy treatments versus a parenteral PVA administered daily for 20 days, healing was similar between the two groups.[50] A large, randomized, controlled trial in Afghanistan showed that one treatment with the FDA-approved device ThermoMed (Thermosurgery Technologies, Inc., Phoenix, AZ), which provides controlled localized current field radio frequency heat directly to the skin lesion, produced results that were comparable to various intralesional PVA treatments and superior to parenteral PVA treatment administered daily for 20 days.[29]

Cryotherapy using liquid nitrogen has been used with variable results: It has a healing rate of 27% to 92% but can cause skin hypopigmentation.[48,49] It was found to be more effective when used with a PVA than when used alone.[46]

Such physical methods as scraping, curettage, or cauterization have been used to treat CL with varying degrees of success. With these methods, however, there is some concern that there could be risk of lymphatic dissemination.[51]

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Intralesional injection of PVA delivers high concentrations of antimony directly to the infected lesions, uses less PVA than parenteral injection, and avoids systemic toxicity. Results, however, show inconsistent efficacy generally proportional to the number of treatments and associated care. In addition, the treatment is time-consuming and painful. In one study, intralesional injection was as effective as daily intramuscular PVA injections and led to faster improvement.[52] The current IND protocol in the United States does not accommodate intralesional use.

PREVENTING INFECTION

Sand flies bite predominately at night. For protection, individuals in endemic areas are advised to wear long sleeves and trousers, to use insect repellents containing DEET (N,N-diethyl-3-methylbenzamide), and to saturate mosquito nets and clothing with permethrin. On average, insect repellents containing 100% DEET will be effective for nine and a half hours; 30% DEET, for six and a half hours; 15% DEET, for five hours; 10% DEET, for three hours; and 5% DEET, for two hours.[43] Controlled-release preparations containing 20% to 35% DEET may be effective for eight to 12 hours or more. Factors such as high temperature and humidity may reduce the duration of a repellent's effectiveness.[53] In general, adults and children over the age of 12 should use preparations containing 25% to 35% DEET.[53]

Since sand flies are smaller than mosquitoes, effective mosquito netting must be finer-mesh (at least 18 holes to the linear inch, which is very warm) and treated with permethrin. In the community or area of operations, known animal reservoirs can be controlled by bulldozing gerbil burrows, destroying infected dogs, or providing the dog population with deltamethrin-saturated collars.

Vaccines against *Leishmania* infection are being investigated, but there are no such products currently available in the United States. In general, recovery from leishmaniasis provides protection from reinfection with the same species. In some parts of the world, this provides the rationale for the immunoprophylactic strategy of scarification with small doses of *L. major* at a body site usually covered by clothing. Although this method, called leishmanization, results in total or partial protection against a subsequent infection, it has been abandoned for the most part due to the risk of occasional severe or persistent lesions and concerns about introducing a live virulent organism into humans.[54,55]

Effective mosquito netting must be finer-mesh (at least 18 holes to the linear inch, which is very warm) and treated with permethrin.

CONTINUING CHALLENGES

As OEF and OIF continue, federal practitioners will encounter more patients with CL. It is usually a self-limited disease, but both diagnosis and treatment pose challenges for U.S. practitioners who have little experience with this type of infection. For new-world CL and old-world leishmaniasis with facial or ear lesions, potential disfigurement, or potential motion restriction due to scarring over joints, the treatment of choice is intravenous sodium stibogluconate, which must be given under the auspices of an IND protocol. For patients at lower risk for poor outcome, alternative treatments may be considered. ●

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